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ORIGINAL ARTICLE

A limited number of medicines pragmatic trials had potential for waived informed consent following the 2016 CIOMS ethical guidelines

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Abstract

Objectives: European regulations do not allow modification or waiver of informed consent for medicines randomized controlled trials (RCTs) where the three 2016 Council for International Organizations of Medical Sciences (CIOMS) provisions are met (consent would be impractical or unfeasible, yet the trial would have high social value and pose no or minimal risk to participants). We aimed to identify whether any such trials of medicines were being conducted in Europe.

Study Design and Setting: This is a survey of all phase 4 ''ongoing'' RCTs on the EU clinical trial register between July 1, 2016 and June 30, 2018, to identify those with potentially high levels of pragmatism. Trials that were excluded were as follows: those conducted on rare diseases; conducted on healthy volunteers (except those assessing vaccines); masked (single-, double-blind) trials; single-center trials; those where one could expect to lead patients to prefer one intervention over the other; and miscellaneous reasons. The degree of pragmatism of the RCTs was self-assessed by trials' investigators by means of the PRECIS-2 tool. Investigators of those trials considered to be highly pragmatic assessed the fulfillment of the three CIOMS provisions. Seven patients assessed the social value of the RCTs. Finally, 33 members of 11 research ethics committees (RECs) assessed the social value of the trials and whether they posed no more than minimal risk to participants. Investigators, patients, and REC members assessed the fulfillment of the CIOMS provisions as ''yes,'' ''not sure'' or ''no.''

Results: Of the 638 phase 4 trials, 420 were RCTs, and 21 of these (5%) were candidates to be pragmatic. Investigators of 15 of these 21 RCTs self-assessed their trial's degree of pragmatism: 14 were highly pragmatic. Of these 14, eight fulfilled the three CIOMS provisions. Assessments by patients and RECs were inconsistent for several trials.

Conclusions: We found few low-risk participant-level pragmatic RCTs that could be suitable for modified or waived participants' informed consent. European regulators should consider amending the current regulation and encouraging the conduct of such trials.

Keywords: Medicines; Phase 4 trials; Pragmatic clinical trial; EU-CTR; Informed consent; Waiver

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What is new?

Key findings

- Seeking patients' written informed consent is a well-recognized barrier to participation in randomized controlled trials (RCTs) with medicines. This study showed that in 2016–2018, about 5% of trials conducted in Europe were low-risk pragmatic RCTs that could have fulfilled the three Council for International Organizations of Medical Sciences (CIOMS) provisions for modification or waiver of participants' informed consent, something that is not acceptable in the current EU clinical trials regulation.

What this adds to what was known?

- This is the first study exploring two critical aspects regarding pragmatic RCTs with medicines: (1) the number of highly pragmatic RCTs actually conducted in Europe as per the trials' investigators self-assessment by means of the PRECIS-2 tool and (2) the hypothetical number of low-risk highly pragmatic RCTs that could have been conducted with a modification or waiver of participants' informed consent, from an assessment conducted by trials' investigators, patients, and members of research ethics committees.

What is the implication and what should change now?

- EU regulators should consider amending the clinical trial regulation to include the possibility of conducting low-risk pragmatic RCTs with a modification or waiver of participants' consent provided it fulfills the three CIOMS provisions and is approved by the relevant research ethics committee. This will most likely ease the recruitment in this type of important social value trials.

1. Introduction

Randomized controlled trials (RCTs) can be described as "pragmatic"—those aimed to inform decision making and hence performed as in (or close to) usual clinical practice—and "explanatory"—aimed to confirm or refute a hypothesis about mechanism of action and, hence, conducted under strict controlled conditions. Most trials have both some pragmatic and some exploratory features [1]. The degree of pragmatism can be assessed with the use of the PRECIS-2 tool [1]. Pragmatic RCTs (pRCTs) are of critical importance to society since they are aimed to answer questions relevant to the real world of available interventions –these being regulated (medicines, devices) and non-regulated (e.g., physiotherapy, psychotherapy) interventions. With regards to RCTs with medicines, trials with a high degree of pragmatism can only be conducted with marketed products (phase 4 trials) prescribed as in usual clinical practice. However, these pRCTs are rare [2].

Pragmatic RCTs (pRCTs) that pose no or minimal incremental risk compared to usual care are known as "low-risk" pRCTs [3]. In the EU clinical trials regulation, this type of trials is labeled as "low-intervention" trials [4]. These trials compare the effectiveness of medicines that are prescribed according to the registered indication or off-label supported by scientific evidence-based data. Furthermore, the eventual additional diagnostic or monitoring procedures established in the trial protocol should not pose more than minimal additional risk or burden to the safety of participants as compared to normal clinical practice [4]. Seeking participants' written informed consent is obligatory in this type of trials in the EU.

The Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines—prepared in collaboration with the World Health Organization—is, with the Declaration of Helsinki, the most important international ethical guidelines for health-related research involving humans. These guidelines provide guidance to investigators on how to apply in practice the ethical principles for research. Since the 1980's, CIOMS guidelines have served as a reference in the conduct of international trials and medical research in low- and middle-income countries [5,6], and as a basis for many International Conference on Harmonization of Technical Requirements for Pharmaceutical for Human Use (the "ICH") guidelines—implemented in the EU, North America and Japan [7]. Through the ICH, CIOMS guidelines have influenced clinical trials regulation in the EU and other jurisdictions. Although they are not legally binding, they have moral validity in many countries and influence research policy in most international funders [6]. The 2016 CIOMS ethical guidelines [8] consider that human research can be conducted with a modification or waiver of participants' informed consent when three provisions are met: the study is unfeasible or impractical without waiving participants' consent, it has important social value, and it will pose no more than minimal risk to participants; the protocol must be approved by the relevant research ethics committee (REC). Although it has been proposed that some low-risk participant-level pRCTs (or low-intervention RCTs) could be entitled to be performed with a modification or waiver of participants' written informed consent [9], this is currently not acceptable following the EU clinical trials regulations [4].

There is a need to encourage and facilitate clinical research integrated in clinical practice. In spite of the potential of new technologies to achieve this, the EU regulations hinder the conduct of pRCTs embedded in clinical practice by requesting the fulfillment of the same requirements than to explanatory RCTs. The aim of this study

was to assess low-risk participant-level pRCTs on common diseases that were being conducted in the EU in 2016−2018 and that could be considered as candidates to modification or waiver of participants' informed consent.

2. Materials and methods

This study comprised 5 steps. First, a search was conducted on the EU Clinical Trials Register (EU-CTR) to identify the RCTs likely to be considered as low-risk participant-level pRCTs. Second, to assess the degree of pragmatism of the trials included in this list, a questionnaire was e-mailed to the trials' investigators (contact persons). Third, with the information obtained, we sent a second questionnaire to the trials' investigators to assess whether they believed that their trials would have fulfilled the three CIOMS provisions. Fourth, the features of the trials that fulfilled the three CIOMS provisions—as per investigators' assessment—were reviewed by a group of patients to assess whether they had ''important'' social value. Finally, this same list of trials was submitted to 12 Spanish RECs to assess whether they have ''important'' social value and whether they posed no more than minimal risk to participants.

The search on the EU-CTR was conducted on August 1−7, 2018 and considered all phase 4 trials that were 'ongoing' between July 1, 2016 and June 30, 2018. The EU-CTR displays all trials assessing medicines conducted in, at least, one center located in the European Economic Area (i.e., EU Member States, Iceland, Liechtenstein, and Norway). We screened the retrieved records of trials for a set of design characteristics that would prevent it from being considered as pRCTs. Therefore, after excluding those trials that did not assess medicines and those phase 3 trials that were erroneously labeled as phase 4, the following trials were excluded in the following order: (1) those conducted on patients with rare diseases; (2) those that were not randomized; (3) RCTs conducted in healthy volunteers (except those conducted to assess vaccines); (4) masked RCTs where the physicians or participants were blinded [2,10,11]—however, when only assessors were blinded, those RCTs were accepted because this feature does not interfere with normal clinical practice; (5) those conducted in a single-center [1,7]; (6) RCTs that compared interventions that could be expected to lead some patients to have preference for one intervention or the other (e.g., device vs. medicine, parenteral medicine vs. oral medicine, o.d. vs. b.i.d., medicine vs. no treatment) because in these cases potential participants should have the chance to be informed to make a decision; and finally, (7) a miscellaneous group comprising RCTs on serious diseases or conditions (e.g., cancer, terminally ill); trials with specific objectives (e.g., amyloid PET; pharmacokinetics/pharmacodynamics) or features (e.g., treatment regimen differing significantly from normal practice) and, as the last reason, industry-sponsored RCTs—ticked as 'commercial' on the EU-CTR—(participants should know when a trial could yield economic gain to the trial's for-profit sponsor). We successively applied these exclusion criteria.

In addition to the EU-CTR, trials' information was searched on ClinicalTrials.gov, ISRCTN and NTR, when the EU-CTR ticked the trial as 'single-blind' (these trials could mask the participant or the assessor) and when other ambiguities or inconsistencies existed in the EU-CTR record. When available, published trials' protocols and trial's websites were also checked.

Data were extracted, reviewed, and rechecked twice by RD-R. No other reviewer assessed trials excluded for reasons that are highly objective (e.g., rare diseases, nonrandomized, healthy volunteers, blinding). CAS independently reviewed all trials excluded because of any other reason (where some subjectivity is possible). Discrepancies between RD-R and CAS assessments were resolved by consensus.

A questionnaire was designed aimed to gather information on the PRECIS-2 tool nine domains [1], current situation on recruitment, and setting (Appendix 1). Because the PRECIS-2 tool is not that widely used among investigators, we decided to ask trials' contact investigators to classify the nine domains as 'yes', 'partially', or 'no'. This questionnaire was sent up to three times during September to October 2018 to one or two trials' contact people; in few cases, we ended up calling contact investigators. A second questionnaire was sent in November 2018 to ask investigators whether they considered that their trials would have fulfilled the three CIOMS provisions regarding modification or waiver participants' informed consent if the EU clinical trial regulations had allowed this; we also asked for the source of the trial's funding (Appendix 2). The list of trials of which the investigators stated that they would have probably or definitely pursued a modification or waiver of participants' written informed consent was sent to a small group of British patients (Appendix 3), and to 12 Spanish university hospital RECs (Appendix 4); RECs were asked to assess the 'important' social value and whether no or minimal risk was posed to participants. The trials' information provided to both patients and RECs were the trials' PRECIS-2 nine domains self-assessment conducted by the investigators and the links to the trials' information posted on EU-CTR and other registries (if available). Contact persons at each REC were asked to recruit two additional members of any background and responsibility within the committee, ensuring both genders were represented. There were three possible answers that each REC could provide to each trial: 'Yes', 'No' and 'Not sure'—this latter acknowledge that the information provided for each trial was limited and that the knowledge of the three assessors could be limited. The patients assessed all trials, whereas each REC was asked to assess half of them, aiming to have each trial assessed by members of at least three RECs.

One author (R.S.), a patient representative, assembled and led a team of seven patients with experience of

scientific research evaluation. They represented both genders, and a range of ages (20–71 years old) and diseases/conditions. Many research funders in the United Kingdom, including the National Institute for Health Research [12], expect or even require patient (and/or public) involvement in the research that they fund, so we felt that having British patients involved in this exercise would be the most appropriate approach. All seven received the same information provided to RECs but were asked to only assess the 'important' social value of the trials (Appendix 3). Again, three possible answers could be given to each trial: 'Yes', 'No' and 'Not sure'—this latter acknowledge that the information provided for each trial was limited and that patients could have limited (or no) experience in the field of one or several trials. Each patient had to assess the trials on their own without discussing them with other participants.

3. Results

We found records for 653 phase 4 trials that were "ongoing" in 2016–2018 on the EU-CTR (Appendix 5). We excluded one observational study and two trials assessing acupuncture and a digital diary and 12 trials that were phase 3 or 3b rather than phase 4 trials: inconsistencies were obvious within the information posted on the EU-CTR or between that of the EU-CTR and that of other registers—in these cases, trials' contact persons provided the correct information.

As shown in Fig. 1, of the 638 'ongoing' phase 4 trials, only 420 were RCTs. Successively applying the exclusion criteria, we ended up with 21 (5%; 21/420) RCTs on common diseases that were candidates to be pragmatic (Table 1).

Most of these 21 trials were conducted in a single country (n = 14; notably, 6 in the Netherlands) and were sponsored by institutions from 8 different member states; 5 trials were on cardiovascular and 4 on infectious diseases and patients undergoing surgical interventions; in 9 trials, the medicines were given orally; most (n = 18) were trials with two treatment arms. The number of sites and participants ranged from 2 to 176 and from 144 to 8,468, respectively; 20 were conducted in hospitals. The recruitment projected time varied from 1 year to 5 years and 1 month. The four trials that started recruiting participants long enough to know if they have met their recruitment expectations were running far behind. Six trials (HOT-ICU, iPROVE-O2, LIBERAL, LQD Study, RAIN, and REBOOT-CNIC) were blinded for outcome assessment.

We found some issues due to the lack of reliable information on the EU-CTR that were solved with that available in other sources (Appendix 6). PRECIS-2 tool self-assessment was conducted by the contact people (including 9 principal investigators) from 15 RCTs (Table 2). Most (10/15) trials were in the 'recruiting' period. All but one (The Eczema Study) were considered to be highly pragmatic. Although all were 'noncommercial' trials, four (out of 14) trials were totally or partially industry-funded,

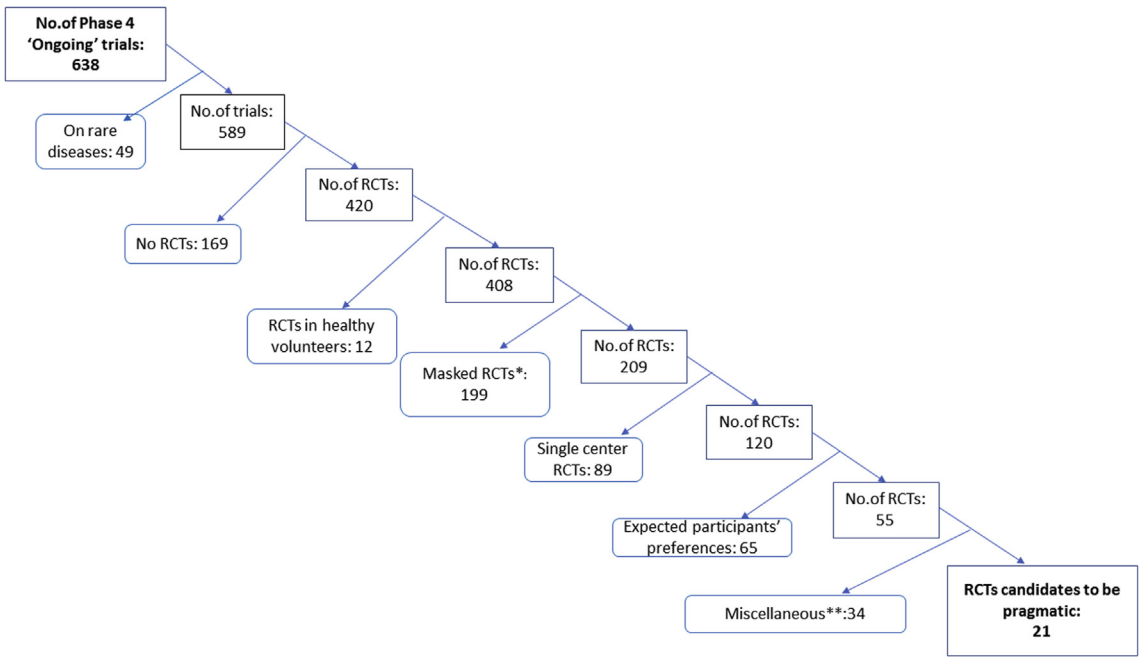

Fig. 1. Flowchart. Trials hosted on the EU-CTR (EU–Clinical Trials Register). From phase 4 "ongoing" trials to randomized controlled trials that were candidates to be pragmatic. *Single-blind: 22; double-blind: 177. Of these latter, based on ClinicalTrials.gov information: triple-blind: 17; quadruple-blind: 39. ** Not usual practice: 15; pharmacokinetics and/or pharmacodynamics: 7; commercial: 6; cancer: 3; terminally ill: 1; amyloid PET: 1; pilot: 1. Abbreviation: RCT, randomized controlled trial.

Table 1. Low-risk phase 4 RCTs on common diseases or conditions, candidates to present a high degree of pragmatism

Trial name/country[a]	EU-CTR/other registry Ref. Nos.	Disease-condition; eligible population	Medicines	Route of administration	Main outcome measure	Time point	Recruitment projected time	No. of centers/ participants	Setting	Sponsor/funding[e]
Compare Crush/ Netherlands	2017-002419-32/ NCT03296540	ST elevated myocardial infarction; adults, elderly	Crushed vs. integral tablets of prasugrel	Oral	Percentage of patients reaching TIMI flow grade 3 or ≥70% ST-segment resolution	Directly post-PCI	3 yr and 6 mo	42/674	Hospital	Research Partnership Cardiologists South Rotterdam, Rotterdam, Netherlands
DiDo/Belgium, France, UK	2011-005274-30/ NCT01944852	Chronic renal insufficiency with continuous ambulatory peritoneal dialysis; elderly	Icodextrin (2 bags) + glucose (1 bag) vs. icodextrin (1 bag) + glucose (2 bags); daily	Intraperitoneal	Percentage of patients stopping 3 bags/day	9 (18[d]) mo	2 yr and 9 mo	30/160	Hospital[e]	Catholic University, Louvain, Belgium/ Private non–for-profit organizations, industry, and patients' association
HIGHLOW Study/ Belgium, Canada, France, Ireland, Netherlands, Norway, USA[c]	2012-001505-24/ NCT01828697	Pregnant patients with history of venous thromboembolism; adults	Intermediate vs. low doses of low-molecular-weight heparin; 4 marketed different LMWH[d]	sc	Recurrent venous thromboembolism (and symptomatic confirmed pulmonary embolism[c])	During pregnancy or in the first 6 wk after delivery	4 yr[c]	69[c]/850 (1,000)[d]	Hospital	Academic Medical Center, Amsterdam University, Amsterdam, Netherlands
HOT-ICU[d]/Denmark, Finland, Iceland, Netherlands, Norway, Switzerland, UK[d]	2017-000632-34/ NCT03174002	Acute hypoxemic respiratory failure; adults, elderly	Low arterial PaO_2 vs. high arterial PaO_2	Inhalation	Mortality	3 mo	2 yr and 9 mo	50/2,928	Hospital[e]	Aalborg University Hospital, Aalborg, Denmark/ Public and private non–for-profit organization
GE-IDE-MucT001-14/ Germany, Hungary	2014-002171-29	Biomarker-negative angina patients with an indication for PCI; adults, elderly	Prasugrel 60 mg vs. clopidogrel 600 mg. Loading single doses.	Oral	Combined outcome of all-cause death, any myocardial infarction, stent thrombosis, urgent revascularization, and stroke	30 days after index PCI	2 yr and 7 mo	8/2,240	Hospital	Hospital of the University of Munich, Munich, Germany
iPROVE-O2/Spain	2016-002936-34/ NCT02776046	Patients scheduled for major abdominal surgery (>2 h) under general anesthesia; adults, elderly	High FiO_2 vs. conventional FiO_2; with perioperative open lung strategy	Inhalation	Surgical site infection as per CDC criteria	7 postoperative days	2 yr and 6 mo	17/756	Hospital[e]	Research Foundation, Clinic Hospital, Valencia[d], Spain/ Industry
LIBERAL/Germany	2016-004446-29/ NCT03369210	Intermediate- or high-risk noncardiac surgery patients; elderly	Liberal transfusions of red blood cell with a post-transfusion target of Hb level of 9–10.5 g/dL vs. restrictive red blood cell transfusions with an Hb target level of 7.5–9 g/dL[d]	iv	Composite of all-cause mortality, AMI, acute ischemic stroke, acute kidney injury, acute mesenteric ischemia, acute peripheral vascular ischemia	90 days after surgery	3 yr and 9 mo	16/2,470	Hospital[e]	University of Goethe, Frankfurt, Germany/ Public
LQD Study/UK	2016-001637-27/ ISRCTN16387615/ NCT03004521	Resistant major depression (single episode or recurrent); adults, elderly	Lithium + existing antidepressant vs. quetiapine + existing antidepressant	Oral	Difference in time to all-cause treatment discontinuation and self-reported longitudinal depressive symptom severity (QIDS-SR)	Over 12 mo after randomization; QIDS-SR, weekly, over 12 mo [13]	2 yr and 3 mo[d]	7[d]/276	Hospital and primary care centers[d]	South London and Maudsley NHS Foundation Trust, King's College London, London, UK/Public
POPular-TAVI/, Belgium, Czechia, Luxembourg, Netherlands,[d]	2013-003125-28/ NCT02247128	Patients undergoing transcatheter aortic valve implantation, elderly	Cohort A: aspirin + clopidogrel vs. aspirin Cohort B: oral anticoagulants + clopidogrel vs. oral anticoagulants	Oral	All bleeding and non–procedure-related bleeding	12 mo [14]	2 yr and 3 mo	8 (17[d])/1,000	Hospital	Dutch Organization for Health Research and Development (ZonMW) and St. Antonius Hospital, Nieuwegein, Netherlands

(*Continued*)

Table 1. Continued

Trial name/country[a]	EU-CTR/other registry Ref. Nos.	Disease-condition; eligible population	Medicines	Route of administration	Main outcome measure	Time point	Recruitment projected time	No. of centers/ participants	Setting	Sponsor/funding[e]
PROGRESS/Greece	2017-002011-33/ NCT03333304	Community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, bacteremia, acute pyelonephritis; adults, elderly	Standard of care antibiotics vs. procalcitonin-guided rule of early stop antimicrobial therapy	iv	Decrease incidence of Clostridium difficile infections and by multidrug-resistant bacteria or infection-related death	6 mo	1 yr	6/280	Hospital[e]	Hellenic Institute for the Study of Sepsis, Athens, Greece/Intramural funds
PRO-SWAP/ Netherlands	2017-002938-23/ NCT03228108	Transrectal prostate biopsy; adults, elderly	Ciprofloxacin vs. rectal culture-guided oral antibiotic prophylaxis	Oral	Clinical infectious complication	Within 7 days after biopsy	3 yr	3/1,618 (1,400)[d]	Hospital[e]	Radboud University Medical Center, Nijmegen, Netherlands/ Public
RAIN/Netherlands	2016-004447-36/ NCT03247920	Probable bacterial infection; neonates	Amoxicillin/Clavulanic switch iv-to-oral vs. iv	iv, oral	Bacterial reinfection	Within 28 days after end of antibacterial treatment[d]	2 yr and 5 mo	15/600 (550)[d]	Hospital	Stichting Rotterdams Onderzoeksconsortium Kindergeneeskunde, Rotterdam, Netherlands
REBOOT-CNIC[b]/Italy, Spain[d]	2017-002485-40/ NCT03596385	Myocardial infarction with or without ST elevation, with LVEF>40% at discharged without previous heart failure; adults, elderly	One of 5 beta-blockers to be prescribed by treating physician vs. no beta-blocker therapy; other therapy as prescribed by treating physician (expect to follow ESC guidelines[e])	Oral	Incidence rate of the composite of all-cause death, reinfarction, or heart failure hospitalization	2.75 yr	2 yr and 3 mo	176/8,468	Hospital[e]	National Center on Cardiovascular Research (CNIC), Madrid, Spain/ Intramural funds
RECOVER study/ Netherlands	2018-001485-42	Laparoscopic colorectal surgery; adults	Low vs. normal pressure pneumoperitoneum with deep neuromuscular blockade on the early recovery	iv	Quality recovery (QoR-40) questionnaire score	24 hours after surgery	1 yr and 6 mo	2/204	Hospital[e]	Rabdoud University Medical Center, Nijmegen, Netherlands/ Industry
REDUCe SWEDE-HEART/Sweden	2017-002336-17/ NCT03278509	Acute myocardial infarction with preserved ejection fraction; adults, elderly	Long-term beta-blockers vs. best evidence-based care with no beta-blockers	Oral	Composite of death of any cause or myocardial infection	Time to event (estimated: max 1-3 yr)	2 yr	36[e]/7,000	Hospital[e]	Karolinska Institute, Stockholm, Sweden/ Public
REMAP-CAP/Australia, Ireland, Netherlands, New Zealand[d]	2015-002340-14/ NCT02735707	Severe community-acquired pneumonia; adults, elderly	Antibiotics (long or short duration) with or without corticosteroids; factorial assignment, adaptive design[d]	iv, oral	All-cause mortality	90 days from enrollment	5 yr and 1 mo	100 (36[d])/6,800	Hospital	University Medical Center, Utrecht, Netherlands
REMINDRA/ Netherlands	2015-004858-17/ NCT02935387	New-onset rheumatoid arthritis; adults, elderly	Taper and stop golimumab followed by taper and stop methotrexate vs. taper and stop methotrexate followed by taper and stop golimumab	sc	Proportion of patients in sustained remission	24 wk after tapering	4 yr and 6 mo	9[e]/267	Hospital[e]	University Medical Center, Utrecht, Netherlands/ Public and Industry

(*Continued*)

Table 1. Continued

Trial name/country[a]	EU-CTR/other registry Ref. Nos.	Disease-condition; eligible population	Medicines	Route of administration	Main outcome measure	Time point	Recruitment projected time	No. of centers/ participants	Setting	Sponsor/funding[e]
SUNSTAR/France	2017-000947-41/ NCT03227419	Rheumatoid arthritis patients with inadequate response to TNF alpha inhibitor; adults, elderly	Abatacept vs. tocilizumab	sc	Clinical disease activity index	Baseline, 3, 6, 12 mo	3 yr	25/224	Hospital[e]	Group of Hospitals of the Lille Catholic Institute, Lomme, France/Public
SYMTRI/Spain	2018-001645-14	Naïve HIV patients; adults	2 fixed dose combinations; 4 active ingredients vs. 3 active ingredients	Oral	Proportion of patients with HIV-1 RNA<50 copies/ml (FDA-defined snapshot algorithm)	48 wk	1 yr and 1 mo	30/316	Hospital[e]	Spanish HIV/AIDS Research Network, Carlos III Research Institute, Madrid, Spain/ Intramural funds
TACSI[b]/Sweden	2017-001499-43/ NCT03560310	Isolated coronary artery bypass in patients with acute coronary syndrome; adults, elderly	Ticagrelor + aspirin vs. aspirin	Oral	Time to major adverse cardiovascular event	12 mo	2 yr	20/2,200	Hospital and registries[e]	Sahlgrenska University Hospital, Gothenburg, Sweden/Public and private non–for-profit organization
The Eczema study/ Netherlands	2017-001525-40	Atopic dermatitis, eczema; children and adolescents	Different strengths of 4 topical steroids	Topical	Changes in disease severity by POEM and EASI	1 and 24 wk	1 yr and 6 mo	36/144	Primary care and home visits[e]	Erasmus Medical Center, Rotterdam, Netherlands

Abbreviations: AMI, acute myocardial infarction; CDC, US Centers for Disease Control and Prevention; EASI, eczema area and severity index; ESC, European Society of Cardiology; FDA, US Food and Drug Administration; FiO_2, inspiratory oxygen fraction; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; PaO_2, partial pressure of oxygen; PCI, percutaneous coronary intervention; POEM, patient-oriented eczema measure; TNF, tumor necrosis factor.

All trials have 2 treatment arms, except DiDo (4 arms), POPular-TAVI (2 cohorts with 2 arms/cohort), and REMAP-CAP (factorial assignment, adaptive design). Data from the EU-CTR unless otherwise stated (as of August 2018).

[a] Where the trial is being conducted.
[b] Self-labeled as 'pragmatic'.
[c] Data from trial's website.
[d] As per Clinicaltrials.gov or ISRCTN information.
[e] Information provided by the trial's contact person.

Table 2. PRECIS-2 tool 9 domains self-assessments by trials' investigators (contact persons) and self-declared ongoing status (as of October to November 2018)

	Pragmatic approach of the trial with regards to the following domains										
Trial name	**Eligibility**	**Recruitment**	**Setting**	**Organization**	**Flexibility (delivery)**	**Flexibility (adherence)**	**Follow-up**	**Primary outcome**	**Primary analysis**	**No. (%) of domains with pragmatic features**	**Ongoing status[a]**
DiDo	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	8 (89)	Active, not recruiting
HOT-ICU	Partially	Yes	Yes	Yes	Yes	NA[b]	Partially	Yes	Yes	6 (75)	Recruiting
iPROVE-O2	Partially	Yes	Yes	Yes	Yes	NA[b]	Yes	Yes	Yes	7 (88)	Active, not recruiting
LIBERAL	Partially	Yes	Yes	Yes	Yes	NA[b]	Partially	Yes	Yes	6 (75)	Recruiting
LQD Study	Yes	Partially	Yes	Yes	Yes	Yes	Yes	Partially	Yes	7 (78)	Recruiting
PROGRESS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (100)	Recruiting
PRO-SWAP	Yes	Yes	Yes	Partially	Yes	Partially	Yes	Yes	Yes	7 (78)	Recruiting
REBOOT-CNIC	Yes	Yes	Yes	Partially	Yes	Partially	Partially	Yes	Yes	6 (67)	Not yet recruiting
RECOVER Study	Partially	Yes	Yes	Partially	Yes	NA[b]	Yes	Yes	Yes	6 (75)	Not yet recruiting
REDUCe SWEDE-HEART	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (100)	Recruiting
REMINDRA	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	8 (89)	Recruiting
SUNSTAR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Yes	8 (89)	Recruiting
SYMTRI	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	8 (89)	Not yet recruiting
TACSI	Yes	Yes	Yes	Yes	Yes	Partially	Partially	Yes	Yes	7 (78)	Recruiting
The Eczema Study	No	No	Yes	Yes	Yes	Partially	No	Partially	Yes	4 (44)	Recruiting

[a] ''Ongoing'' on EU-CTR database comprises trials not yet recruiting, those actively recruiting, and those that are active, once recruitment has been completed.
[b] This is a surgical trial assessing medicines.
[c] Because the drugs under study are delivered in the investigator's office, instead of, as in usual clinical practice, in the hospital pharmacy.

hence being 'investigator-initiated' RCTs. Investigators assessed that five trials fulfilled the three provisions and were not sure on the unfeasibility or impracticability of three trials: these eight trials were those subjected to the assessment from RECs members and patients (Table 3).

Results of patients' assessments (Table 4) showed that out of 56 answers, 25 were 'Yes', 24 'Not sure' and seven 'No'. Notably, PROGRESS received a high (6/7) support of its important social value, whereas SYMTRI got no support at all.

Thirty-three individuals, members of 11 different university hospital RECs with a long-standing record on clinical trials assessments and several of them serving more than one hospital, were involved in this exercise. Among these individuals, there were physicians of various specialties, scientists (Molecular Biology, Pharmacy), nurses, a patients' representative, and a lay member (social worker). The answers provided by these REC members occasionally showed different results for the same trial (Table 4). Some, like PROGRESS, REDUCe-SWEDE HEART, REMINDRA, SUNSTAR, and SYMTRI, received fairly similar assessments; while others like DiDo, REBOOT-CNIC, and RECOVER received diverse results. ''Not sure'' was chosen by 10 RECs in 7 of the 8 trials, and ''No'' by 3 RECs in 2 trials.

4. Discussion

We have conducted an exercise to estimate the number of ongoing RCTs in the EU that would have been candidates to a modification or waiver of participants' informed consent, if the EU regulation had accepted it. Out of 420 RCTs that were posted as ongoing on the EU-CTR, only 5% (21/420) could be regarded as pragmatic. Furthermore, of those trialists who responded to our request, 14 of 15 rated their trials as highly pragmatic through the evaluation made with the PRECIS-2 tool [1] and only 8/14 thought their trials also fulfilled the three CIOMS provisions for a modification or waiver of participants' informed consent. Thus, in this hypothetical scenario, only some 1.9% [8/420] would have been candidates to have the informed consent process modified or waived.

In this exercise, we have also probed the views of REC members. Their assessments varied substantially, although more in some trials than in others. This was probably because RECs were provided only with the information posted on the registries and the investigators' PRECIS-2 tool self-assessment; yet, in real life, the full protocol, other supplemental information, and, critical for the assessment, the information supporting the fulfillment of the three CIOMS provisions would have been submitted to the REC. Furthermore, for this type of trials, investigators might have been required to attend the REC meeting to answer queries in the presence of all REC members. Finally, in the assessments that we obtained by patients, we got similar assessments to those of RECs in some trials, but with few more negative and ''Not sure'' answers. This is not surprising when nonexperts have to individually assess incomplete information.

Table 3. Three CIOMS provisions for modification or waiving participants' informed consent: self-assessment by trials' investigators (contact persons)

	Investigators' self-assessment		
Clinical trial	**Art. 10—Provision 1: This trial would not be feasible or practicable to carry out without the modification or waiver of the informed consent***	**Art. 10—Provision 2: This trial has important social value**	**Art. 10—Provision 3: This trial poses no more than minimal risks to participants**
DiDo	Yes	Yes	Yes
HOT-ICU	No	Yes	Yes
iPROVE-O2	No	Yes	Yes
LIBERAL	No	Not sure	No
LQD Study	No	Yes	Yes
PROGRESS	Not sure	Yes	Yes
PRO-SWAP	No	Yes	Yes
REBOOT-CNIC	Yes	Yes	Yes
RECOVER Study	Yes	Yes	Yes
REDUCe SWEDE-HEART	Not sure	Yes	Yes
REMINDRA	Yes	Yes	Yes
SUNSTAR	Not sure	Yes	Yes
SYMTRI	Yes	Yes	Yes
TACSI	No	Yes	Yes

Abbreviation: CIOMS, Council for International Organizations of Medical Sciences.

* Yes: the trial would not be feasible without the modification or waiver; No: the trial would be feasible without the modification or waiver.

Table 4. CIOMS provisions for modification or waiver of participants' informed consent: assessment by members of research ethics committees (n = 11) and patients (n = 7)

	Assessment by research ethics committees' members						Patients' assessment (n=7)		
	Art. 10—provision 2: This trial has important social value			Art. 10—provision 3: This trial poses no more than minimal risks to participants			Art. 10—provision 2: This trial has important social value		
Clinical trial (# of RECs assessing the trial)	Yes	Not sure	No	Yes	Not sure	No	Yes	Not sure	No
DiDo (5)	2	3	0	3	2	0	1	5	1
PROGRESS (5)	5	0	0	4	1	0	6	1	0
REBOOT-CNIC (5)	4	1	0	2	1	2	2	3	2
RECOVER study (5)	2	2	1	1	3	1	3	4	0
REDUCe SWEDE HEART (6)	6	0	0	3	3	0	5	1	1
REMINDRA (6)	6	0	0	6	0	0	4	3	0
SUNSTAR (6)	4	2	0	5	1	0	4	3	0
SYMTRI (6)	5	1	0	4	2	0	0	4	3

Abbreviation: CIOMS, Council for International Organizations of Medical Sciences.

4.1. Limitations

The main limitation of this study was its nature: this was an exercise based on real data (phase 4 trials), but placing all participants (trials' investigators, RECs members, and patients) in a hypothetical scenario. Additional limitations reflect the quality of the data and selection criteria. The data retrieved from the EU-CTR were sometimes scarce, inconsistent, and even wrong. In some trials, we could complete the information from registers such as ClinicalTrials.gov and ISRCTN. Inconsistencies between information posted on EU-CTR and ClinicalTrials.gov have been previously shown [15]. Our selection criteria were conservative, and some additional RCTs may have been included. However, it is unlikely that participants' informed consent can be modified or waived unless an RCT is highly pragmatic. Some authors label trials as pragmatic if they show one or two pragmatic features [16], but this is not enough to ensure that the trial resembles normal clinical practice [2]. Moreover, some consider that single-center RCTs can be pragmatic; however, single-site RCTs tend to provide larger treatment effects than multicenter trials [17,18] and may lack generalizability and applicability [1,2].

4.2. Social value of pragmatic RCTs

The social value of a pRCT—as of any other research with human subjects—refers to its ability to gather data and knowledge that will (have the potential to) improve individual or public health [4,19,20]. This depends on the resources needed to conduct the trial and the extent to which it poses risks to participants that are not balanced by potential benefits [20]. Yet, there is not a systematic way to assess the social value of a trial; let alone what "important" social value means. It has been proposed that a meeting between investigators and patients to assess the social value of the intervention should be held before submitting the trial protocol to the relevant REC [21]. Patients should be involved in the complete life cycle of a clinical trial: from protocol development to regulatory benefit/risk assessment [12,22–24]. When dealing with low-risk pRCTs, patients' contribution is especially important in the design and the choice of study end points, although these latter will be mainly dictated by usual clinical practice. Because some trials could be financed by industry, patients should appraise the "important" social value before this type of investigator-initiated trial is discussed with potential industry sponsors.

Pragmatic RCTs are critical to generate comparative effectiveness, which address clinical gaps that could inform medical decision making in usual care [25]. Our analysis shows that there is currently a dearth of medicines low-risk participant-level pRCTs in Europe that might be candidates for waiving informed consent. However, this situation may change if the EU regulation accepts that some trials could be conducted with a modification or waiver of informed consent. Investigators should be educated on what to expect from this type of RCT. Even prominent trialists have not yet comprehended the main features and objectives of low-risk pRCTs and still assess their usefulness from a typical explanatory trial perspective [26]. Training of REC members should also be included in the agenda. The precedent of having cluster RCTs conducted with a simplified (ie, modified) informed consent in the EU should be helpful.

4.3. Recruitment in low-risk pragmatic RCTs

Although there are a variety of reasons for poor recruitment in low-risk pRCTs, seeking patient's consent is a well-recognized barrier to participation [27–29]. Common reasons for recruitment failures in early terminated RCTs were overestimation of the number of eligible patients, prejudices against effectiveness of interventions assessed, and high burden for recruiters and participants [30]. These reasons are obviated in low-risk participant-level pRCTs

with medicines; if seeking participants' written informed consent is modified or waived, which is a concern for both patients and physicians [26], recruitment in the projected time period may significantly increase.

5. Conclusions

The EU regulation should be amended to accept the modification or waiver of participants' informed consent in certain low-risk pRCTs—as both the US [31] and Canadian [32] regulations do—when certain requirements are met. The three CIOMS provisions are similar to the requirements that the US and Canadian regulations ask for [2]. In fact, in 2017, the US FDA stated that will accept any waiver of informed consent granted by an institutional review board for minimal risk clinical research [33]. But it does not suffice to have the clinical trials regulations of all developed countries accepting this type of waiver of participants' informed consent. To be aligned with the CIOMS guidelines, and to have a common approach from the ethical standpoint, the World Medical Association should consider amending the Declaration of Helsinki to accept the modification or waiver of participants' consent with the same three CIOMS requirements. Making pRCTs easier to do may allow obtaining more reliable real-world data from a larger number of relevant RCTs.

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Supplementary data

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